07-cv-11614(JGK)

United States Court of Appeals for the Federal Circuit

2010-1432

MITSUBISHI CHEMICAL CORPORATION and
MITSUBISHI TANABE PHARMA CORPORATION,

Plaintiffs-Appellees,

and

ENCYSIVE PHARMACEUTICALS INC.,

Plaintiff-Appellee,

and

GLAXO GROUP LIMITED, SMITHKLINE BEECHAM PLC,
and SMITHKLINE BEECHAM CORPORATION
(doing business as GlaxoSmithKline),

Plaintiffs-Appellees,

v.

BARR LABORATORIES, INC. and PLIVA-HRVATSKA D.O.O.,

Defendants-Appellants.

Judgment

ON APPEAL from the United States District Court for the Southern District of New York

in CASE NO. 07-CV-11614.

This CAUSE having been heard and considered, it is

ORDERED and ADJUDGED:

AFFIRMED

ENTERED BY ORDER OF THE COURT

DATED AUG - 2 2011

Jan Horbaly, Clerk

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UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

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NOTE: This disposition is nonprecedential.

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Defendants-Appellants.

2010-1432

Appeal from the United States District Court for the Southern District of New York in Case No. 07-CV-11614, Judge John G. Koeltl.

Decided: August 2, 2011

DAVID G. CONLIN, Edwards Angell Palmer & Dodge LLP, of Boston, Massachusetts, argued for all plaintiffs-appellees. With him on the brief for plaintiffs-appellees Mitsubishi Chemical Corporation, et al. were KATHLEEN B. CARR, DAVID COTTA, ADAM P. SAMANSKY and THOMAS H. WINTNER; and ANTHONY J. VIOLA, of New York, New York. Of counsel were ANDRE K. CIZMARIK and BARBARA L. MOORE. On the brief for plaintiff-appellee Encysive Pharmaceuticals Inc were MARTIN L. KATZ and JEFFREY M. DRAKE, Wood Philips Katz Clark & Mortimer, of Chicago, Illinois. Also on the brief for defendants-appellees Glazxo Group Limited, et al were WILLIAM F. LEE, LISA J. PIROZZOLO and CHRISTOPHER R. NOYES, Wilmer Cutler Pickering Hale and Dorr LLP, of Boston, Massachusetts.

STEVEN H. REISBERG, Willkie Farr & Gallagher LLP of New York, New York, argued for the defendants-appellants. With him on the brief were THOMAS J. MELORO, JR. and HEATHER M. SCHNEIDER.

Before BRYSON, DYK, and PROST, *Circuit Judges*.

BRYSON, *Circuit Judge*.

Barr Laboratories, Inc., and Pliva-Hrvatska d.o.o. (collectively, "Barr") appeal from a judgment that Barr infringed each of the four claims of U.S. Patent No. 5,214,052 ("the '052 patent"), assigned to plaintiff Mitsu-

bishi Chemical Corporation (together with other plaintiffs, "Mitsubishi"). We affirm.

I

Argatroban, also known as argipidine, is a drug that acts as an anticoagulant by inhibiting the enzyme thrombin. Argatroban is clinically useful in the treatment of heparin-induced thrombocytopenia, a condition caused by the more widely used anticoagulant heparin. Argatroban's structure and utility as an anticoagulant have been known since at least the early 1980s. Argatroban is a zwitterion, i.e., a molecule with both positive and negative regions of electrical charge. Zwitterions generally have low aqueous solubility at neutral pH levels, with higher solubility in very acidic or very basic solutions. Argatroban's low aqueous solubility at neutral pH levels presents problems for its use in pharmaceutical applications that require administration of high concentrations of the drug.

The '052 patent issued to Mitsubishi in 1993 as a continuation of an application filed in 1988. The specification of the '052 patent explains that the solubility of argatroban increases dramatically when a saccharide and ethanol are added to an aqueous solution. The '052 patent has four claims:

> 1. A method for dissolving an arginineamide, comprising:
>
> dissolving [argatroban] and/or its salt in a solvent containing ethanol, water and a saccharide.
>
> 2. The method according to claim 1, wherein the saccharide is at least one member selected from

> the group consisting of sorbitol, glucose, glycerin and sucrose.
>
> 3. A pharmaceutical composition for injection, comprising:
>
> > [argatroban] and/or its salt together with ethanol, water and a saccharide.
>
> 4. The composition according to claim 3, wherein the saccharide is at least one member selected from the group consisting of sorbitol, glucose, glycerin and sucrose.

Mitsubishi has marketed Argatroban Injection, a product meeting the limitations of claims 3 and 4, since the U.S. Food and Drug Administration ("FDA") approved Mitsubishi's New Drug Application No. 20-883 in 2000. Argatroban Injection consists of a high concentration of argatroban dissolved in a solution of ethanol, water, and sorbitol at a pH between 3.2 and 7.5.

Barr filed an Abbreviated New Drug Application ("ANDA") to market a generic version of Argatroban Injection and notified Mitsubishi of the ANDA in late 2007. Mitsubishi promptly filed suit against Barr, alleging direct and indirect infringement of the '052 patent. In the district court, the parties stipulated that the commercial manufacture, use, importation, sale, or offer for sale of the product described in Barr's ANDA would infringe all four claims of the '052 patent; Barr defended by contending that the four asserted claims were invalid.

Barr made two arguments as part of its invalidity defense. It first contended that each of the claims is anticipated by a Japanese article published in 1986 by a Mitsubishi employee, Toshihiro Yamamoto. In the alter-

native, Barr argued that all of the '052 claims would have been obvious over a combination of several references other than the Yamamoto article.

In the course of the litigation, the parties disputed the appropriate English translation of a single sentence in Yamamoto describing the preparation of an argatroban solution that was administered to laboratory rats for experimental purposes. The district court considered four translations of the original Japanese text. After examining each translation, the court concluded that the only reliable translation was that of Mitsubishi's expert, Martin Cross. Mr. Cross translated the relevant sentence as follows: "In 7.5% D-sorbitol-4% ethanol, an argipidine solution dissolved under hydrochloric acid acidity (pH 1.5 to 1.7) was intraperitoneally administered at a dosage of 1 ml/kg, 15 minutes before common carotid artery occlusion."

Using Mr. Cross's translation, the district court determined that Yamamoto does not anticipate any claim of the '052 patent. The court found that claims 1 and 2 are not anticipated because a person of ordinary skill in the art would have understood Yamamoto to teach dissolution of argatroban in hydrochloric acid alone, i.e., without ethanol or a saccharide. The court credited testimony to that effect by Mitsubishi's expert witness, Dr. Stephen Byrn. The court noted that Dr. Byrn's testimony was corroborated by one of the inventors of the '052 patent, Tatsuo Nomura, a native Japanese speaker, who testified that the disputed sentence from Yamamoto should be understood to mean "in hydrochloric acid the [argatroban] was dissolved and after that it's been put into D-sorbitol and ethanol."

Based on that evidence, the district court found that the language "In 7.5% D-sorbitol-4% ethanol" in the Yamamoto article refers to "how the [argatroban] solution was administered, not how it was dissolved." The court concluded that a person of ordinary skill in the art at the time would have understood the Yamamoto reference to mean that the argatroban was dissolved in acid, "with ethanol and sorbitol added after the argatroban was already dissolved." The court discredited contrary testimony by Barr's expert witness, Dr. Thomas Needham. The court found that Dr. Needham's original interpretation of Yamamoto was "scientifically implausible," and that his revised interpretation involved a lengthy series of steps that would have been explicitly disclosed in the Yamamoto article if the article had intended to describe a composition of the sort recited in claims 1 and 2.

The district court also concluded that Yamamoto does not anticipate claims 3 and 4 of the '052 patent because the solution disclosed in Yamamoto is not a "pharmaceutical composition for injection." The court construed the term "pharmaceutical composition for injection" as "a composition that is suitable for treating medical conditions by injection." The court credited Dr. Byrn's testimony that in order to be suitable for injection into human patients, a pharmaceutical composition must have a pH above 3. The court determined that the solution in Yamamoto, which has a pH between 1.5 and 1.7, is not a pharmaceutical composition for injection because it is too acidic to be suitable for administration to human patients.

The district court then addressed Barr's obviousness argument. At trial, Barr had asked the court not to consider Yamamoto for purposes of obviousness. Instead, Barr relied on several combinations of nine other prior art references. Four of those references discuss argatroban,

but the court concluded that those references "are not focused on argatroban's solubility or any particular methods of formulating argatroban." In particular, the court did not find anything in those references that suggested the use of ethanol or a saccharide as a component of a solvent for argatroban.

The other five references relied on by Barr address solvent systems more generally. Those references discuss solvent systems that include ethanol, water, and a saccharide. The court concluded, however, that the references did not provide any direction to a person of ordinary skill in the art to use that co-solvent combination to dissolve argatroban. Three of the references disclose numerous solvent systems, and the court found that none of them would have directed a person of ordinary skill in the art to use the particular co-solvent system claimed in the '052 patent. The other two references concern dissolution of compounds whose solubility profiles are different from those of zwitterions.

The district court determined that Barr had not met its burden to show by clear and convincing evidence that the prior art references would have motivated one of ordinary skill in the art to dissolve argatroban in a solvent containing ethanol, water, and a saccharide. In addition, the court concluded that secondary considerations such as commercial success and long-felt need supported its conclusion that the '052 claims would not have been obvious. Barr appeals from the court's rulings on validity.

II

A

Barr argues that Yamamoto anticipates each claim of the '052 patent. As part of its argument, Barr challenges the district court's adoption of Mr. Cross's translation of the sentence in Yamamoto that describes the preparation of the argatroban solution. The court found Mr. Cross's translation reliable because it was corroborated by a native Japanese speaker and independently corroborated by Dr. Byrn's explanation of how the composition disclosed in Yamamoto was prepared. The court was also persuaded by Mr. Cross's explanation of how his translation comported with standard Japanese sentence structure.

The district court did not find any of the remaining translations reliable. The court discredited the translation of Barr's expert Charles Aschmann because neither he nor Barr's other translation expert, Gregor Hartmann, could identify source text in the original Japanese corresponding to a portion of Mr. Aschmann's translation. Mr. Hartmann himself produced two translations of Yamamoto, but the court discredited his final translation because Mr. Hartmann acknowledged significant errors in his original version and because he had not consulted with a native Japanese speaker while preparing his translation. Finally, the court discredited a translation that Mitsubishi submitted to the FDA ("the FDA translation") as part of its New Drug Application for Argatroban Injection. The court was persuaded by Mr. Cross's testimony that the FDA translation contained several errors.

Barr points out that the FDA translation and Mr. Aschmann's translation, unlike the Cross translation,

were not prepared for purposes of this litigation. Barr also relies on the testimony of Mr. Aschmann and Mr. Hartmann that the relevant sentence in Yamamoto was straightforward to translate, which contrasted with the testimony of Mr. Cross, who said that he found the translation difficult. Finally, Barr argues that the district court did not properly interpret the meaning of two Japanese words in the relevant sentence.

The fact-finder's selection of a particular translation as the best translation of a foreign language reference raises pure questions of fact. *See Hodosh v. Block Drug Co., Inc.*, 786 F.2d 1136, 1142-43 (Fed. Cir. 1986); *see also Gray v. Noholoa*, 214 U.S. 108, 112 (1909). The district court's selection of the appropriate translation in this case was based in large part on a credibility determination, and such determinations are "virtually never" overturned for clear error. *Honeywell Int'l, Inc. v. Hamilton Sundstrand Corp.*, 523 F.3d 1304, 1314 (Fed. Cir. 2008), quoting *Anderson v. City of Bessemer City*, 470 U.S. 564, 575 (1985). Although Barr contends that Mr. Cross's translation should be disregarded because it was prepared for purposes of litigation, that is not a sufficient reason to conclude that the district court's choice of the Cross translation was clearly erroneous. Barr's remaining arguments relate to inferences drawn from the competing testimony of expert witnesses. The district court is in the best position to draw those inferences, and we find substantial evidentiary support for the court's acceptance of Mr. Cross's translation and its rejection of the other translations.

Barr next argues that even accepting Mr. Cross's translation of the Yamamoto reference, Yamamoto anticipates the two method claims of the '052 patent, claims 1 and 2. Barr challenges the district court's construction of

the term "dissolving" in claim 1. The court found that claim 1 is limited to compositions in which argatroban is completely dissolved in a solvent that contains ethanol, water, and a saccharide, i.e., no further dissolution of argatroban takes place once those three co-solvents are present in the composition. Barr contends that claim 1 covers any system in which some argatroban is dissolved in a solvent containing ethanol, water, and a saccharide, even if most of the argatroban in the solution has been dissolved previously in another solvent system.

We need not resolve this dispute, because Yamamoto fails to anticipate claim 1 or claim 2 under either construction of the term "dissolving." The district court credited the testimony of Dr. Byrn and Mr. Nomura that Yamamoto contemplated that hydrochloric acid would be used to completely dissolve a particular quantity of argatroban, and only then would ethanol and sorbitol be added to the solution. Under Dr. Byrn's interpretation of the Yamamoto article, Yamamoto would not anticipate claims 1 and 2 under either the district court's claim construction or the construction proposed by Barr.

Barr contends that Dr. Byrn's reading of Yamamoto would require hydrochloric acid to be added to the solution both at the outset and again after ethanol and sorbitol were added, in order to adjust the pH of the solution to a final level between 1.5 and 1.7. Barr argues that the record contains no plausible explanation for why a person of skill in the art would choose to add hydrochloric acid to the solution in two separate steps. However, the district court discredited the competing method of preparation proffered by Dr. Needham because his first proposed method was scientifically impossible, his second method involved a nine-step sequence that would be expected to have been disclosed by the reference, and he admitted in a

deposition that he did not know how a person of skill in the art would have interpreted Mr. Cross's translation of Yamamoto. Even if the method of preparation disclosed in Yamamoto, as translated by Mr. Cross, is subject to multiple interpretations, Barr has not shown that Dr. Byrn's interpretation is implausible. Moreover, the district court took note of the fact that Yamamoto's description of the argatroban solution was quite cryptic because, as both experts agreed, Yamamoto was focused on the pharmacological activity of the argatroban molecule, rather than on "argatroban's solubility or on treating the rats." In order to anticipate, the teaching of a reference must be clear and unambiguous. *In re Turlay*, 304 F.2d 893, 899 (CCPA 1962). Because Yamamoto does not clearly teach the methods set forth in claims 1 and 2 of the '052 patent, Barr has not shown that claims 1 and 2 are anticipated by Yamamoto.

B

Barr also contends that Yamamoto anticipates the two product claims of the '052 patent, claims 3 and 4. Barr's argument focuses on the phrase "pharmaceutical composition for injection" in the preamble of claim 3. The district court construed "pharmaceutical composition for injection" to mean "a composition that is suitable for treating medical conditions by injection." Barr proffers the following construction: "a medicinal drug composition that can be administered by injection." Barr explains that the word "medicinal" in its construction modifies only the word "drug," and that claim 3 therefore covers any composition that includes a "medicinal drug," i.e., argatroban, along with ethanol, water, and a saccharide, regardless of whether it can be injected into a patient with therapeutic effect.

In support of its construction, Barr cites to our decision in *Novartis Pharmaceuticals Corp. v. Eon Labs Manufacturing, Inc.*, 363 F.3d 1306 (Fed. Cir. 2004). In that case, this court determined that a composition claim to a "hydrosol . . ." was limited to "a medicinal preparation . . . prepared outside the body." *Id.* at 1311. The court found support for that narrow construction in the patent specification, which referred to the claimed hydrosol as a "pharmaceutical composition" prepared as an "injectable solution." *Id.* at 1310. The court cited a dictionary definition of the noun "pharmaceutical" as meaning "medicinal drug." *Id.*, quoting *Webster's Third New International Dictionary* 1694 (2002). However, as its ensuing claim construction demonstrated, the court in *Novartis Pharmaceuticals* applied the term "pharmaceutical" to the entire "preparation" claimed. *Cf. Forest Labs., Inc. v. Abbott Labs.*, 239 F.3d 1305, 1311 (Fed. Cir. 2001) (a drug "may be part of a pharmaceutical composition, but it is a distinct component of that composition").

The problem with Barr's construction is that the word "pharmaceutical" in claim 3 modifies the entire "composition" referred to in the claim, not simply the argatroban component of the composition. Claims to "pharmaceutical compositions" are typically distinct from claims to medicinal compounds themselves. *See Forest Labs.*, 239 F.3d at 1311. Each of the constituent parts of the composition must be pharmaceutically acceptable, although only the composition as a whole needs to be medicinal in nature. *See Schering Corp. v. Geneva Pharm.*, 339 F.3d 1373, 1382 (Fed. Cir. 2003) (a "pharmaceutical composition" includes a drug along with a "pharmaceutically acceptable carrier"); *In re Gardner*, 427 F.2d 786, 787 (CCPA 1970) (a "pharmaceutical composition" is an active compound "in a suitable pharmaceutical carrier"). The specification of the '052 patent makes clear that "*[t]he solution* contain-

ing any of the [argatroban] in the solvent of alcohol and water and optionally saccharide thus obtained *can constitute the pharmaceutical composition* of the invention." '052 patent, col. 4, ll. 27-31 (emphases added). The district court correctly determined that the term "pharmaceutical" is relevant to the entire composition disclosed in claim 3, not just to the argatroban component.

Significantly, the district court refused to limit claim 3 to those compositions that are "safe, effective, and reliable for use in humans." *In re Krimmel*, 292 F.2d 948, 954 (CCPA 1961). The specification does not require this restrictive construction, nor is this property necessary for patentability. *See In re '318 Patent Infringement Litig.*, 583 F.3d 1317, 1324 (Fed. Cir. 2009) ("human trials are not required for a therapeutic invention to be patentable"). Instead, the court imposed a "minimal requirement that a composition meeting claim 3 must have some medicinal aspect or must pertain to treatment of a clinical indication." We agree with Mitsubishi that the claim extends only to those compositions with "some medicinal aspect."[1]

Barr correctly points out that claim 3 is structured as a "comprising" claim that reads on compositions that include components beyond those explicitly claimed. While claim 3 is open-ended, the addition of new compounds to the composition that would defeat the "phar-

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[1] Barr briefly argues that the term "pharmaceutical composition" should not be read to limit claim 3 at all because it appears in the preamble to the claims. *See Am. Med. Sys., Inc. v. Biolitec, Inc.*, 618 F.3d 1354, 1358-59 (Fed. Cir. 2010). Barr did not make that argument before the district court, however, and therefore cannot raise it for the first time on appeal. *See Conoco, Inc. v. Energy & Envtl. Int'l, L.C.*, 460 F.3d 1349, 1358-59 (Fed. Cir. 2006).

maceutical" character of the overall composition would move the composition outside the scope of the claimed invention. As the district court noted, Barr's claim construction would allow a "plainly toxic composition, such as a cleaning fluid or a pesticide," to meet the limitations of claim 3, even though such a composition would not be medicinal under any definition of that word. *See, e.g.*, *Webster's Third New International Dictionary* 1402 (defining "medicinal" as "tending to cure disease or relieve pain," "sanative," "having wholesome effect," or "salutary"). We therefore reject Barr's attempt to broaden the phrase "pharmaceutical composition for injection" to cover any composition that includes a medicinal product, regardless of its suitability for injection into humans. To the contrary, a "pharmaceutical composition," as claimed in the '052 patent, is a composition consisting of a medicinal drug in a pharmaceutically acceptable carrier.

The district court concluded that the argatroban preparation described in Yamamoto is not a "pharmaceutical composition" because it is too acidic to be injected into a human patient. The court found that a pH of 1.5 to 1.7 "is an extremely low pH . . . which is not acceptable for use in a medicine." The court based its conclusion on testimony by expert witnesses of both parties. Dr. Byrn testified that a solution injected at a pH below 3 could cause extreme pain and tissue damage. He also testified that he would not consider the preparation used in Yamamoto to be a medicine. Similarly, Dr. Needham testified that "there are pH ranges that should not be included in an injectable." The district court also found it probative that Barr did not identify any intravenous drug compositions having a pH range similar to that of the composition identified in Yamamoto. Barr does not challenge those findings of the district court; rather, it relies solely on its claim construction argument. Barr has

not demonstrated by clear and convincing evidence that Yamamoto disclosed an argatroban composition with a pharmaceutically acceptable carrier.

Finally, Barr argues that claims 3 and 4, as construed by the district court, would be invalid for lack of enablement. We disagree. Under the proper construction of "pharmaceutical composition," as set forth above, the claims are clearly enabled. The specification of the '052 patent discloses methods of preparing three sample solutions containing argatroban, ethanol, water, and a saccharide to be administered by injection. '052 patent, col. 5, line 47, to col. 6, line 15. The examples mention only those four components of the composition, in addition to a diluting solution that is "weak[ly] acidic." *Id.*, col. 5, ll. 56-57; col. 6, ll. 14-15. The specification notes that the compositions "may contain stabilizer, buffer, preservative and the like which are acceptable for the injection . . . ." *Id.*, col. 4, ll. 43-44. Because the specification provides straightforward guidance for preparation of the claimed pharmaceutical compositions, it enables claims 3 and 4.

III

Barr briefly argues in the alternative that the claims of the '052 patent are obvious over a combination of prior art references. Barr first cites U.S. Patent No. 4,258,192 ("the '192 patent"), issued in 1981, which discloses the dissolution of argatroban in a solution of water and glucose. Barr argues that it would have been obvious to a person of ordinary skill in the art to add ethanol to the solution disclosed in the '192 patent. The district court found to the contrary, however, based on testimony by experts for both sides. Dr. Byrn testified that "a person in 1987 would expect that ethanol would depress solubility of argatroban in water" because argatroban is a zwit-

terion, and Dr. Needham admitted that the prior art suggested that the solubility of zwitterions is reduced by the addition of ethanol. The court did not clearly err in concluding that the prior art taught away from the use of ethanol to dissolve argatroban.[2]

Barr next points to a 1984 article by Matsui that discloses argatroban dissolved in high concentrations in an "acidic ethanol solution." Barr does not argue that it would have been obvious to add a saccharide to the solution disclosed in Matsui. Instead, Barr contends that Matsui teaches the addition of ethanol to the aqueous solution of argatroban and glucose disclosed in the '192 patent. The district court found that Barr had not demonstrated that a person of ordinary skill in the art would have viewed ethanol (as opposed to acid) as being responsible for dissolving the argatroban in the solution disclosed in Matsui, and Barr makes no argument on appeal to challenge that finding.

Finally, Barr points out that several prior art references disclose solvent systems that include ethanol, water, and a saccharide. However, Barr does not challenge the district court's finding that those references are not specific to argatroban or, more generally, to zwitterions. The district court did not credit Dr. Needham's testimony that a person of ordinary skill in the art would have been directed to the specific co-solvent system disclosed in the '052 patent, because there were a very large number of such systems disclosed in the prior art. Barr

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[2] In its reply brief, Barr challenges Dr. Byrn's testimony that ethanol was known to reduce the solubility of zwitterions such as argatroban. Barr did not raise that argument in its opening brief, and we therefore decline to consider it. *See SmithKline Beecham Corp. v. Apotex Corp.*, 439 F.3d 1312, 1319 (Fed. Cir. 2006).

has pointed to no evidence in the record that undermines the court's factual finding that references disclosing numerous solvent systems would not have taught the use of ethanol, water, and a saccharide as a solvent system for dissolving argatroban.

Because Barr has failed to show that the district court clearly erred in finding that the claims of the '052 patent are not anticipated and has failed to show that those claims would have been obvious, we uphold the judgment of the district court.

AFFIRMED